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EXAMINER	
BALASUBRAMANIAN, VENKATARAMAN	
ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 11/04/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/530,101	GUDMUNDSSON ET AL.	
	Examiner	Art Unit	
	Venkataraman Balasubramanian	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 October 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *8* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7 and 9-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/1/05,9/6/05,10/17/05*
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-22 are pending.

Election/Restrictions

Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

Group I, claims 1-7 and 9-22, drawn to compound of formula I, wherein Y is N, namely pyrimidine compounds, process of making, composition and method of use

Group I, claims 1-6 and 8-22, drawn to compound of formula I, wherein Y is CH, namely pyridine compounds, process of making, composition and method of use

The inventions listed as Groups I, II and III do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The requirement for unity of invention is two-fold: (1) common utility and (2) sharing a substantial structural feature disclosed as being essential to the utility. Both these conditions are to be met with.

Groups I and II are independent and distinct from each other because they are directed to structurally dissimilar compounds that lack common core namely pyrimidine versus pyridine cores. Consequently, the groups require separate prior art searches. They can be made and used independently. Art, which may render obvious or anticipate one of the groups would not necessarily do the same for the other group as evidenced

by the references cited in the International Search Report. Each can support a patent, as the compounds of each group are capable of being utilized alone not in combination with other members listed in the Markush group.

Except for few carbon atoms and a pyrazolo ring, all structural features are varied and therefore the core groups do not share the same structural feature essential for the disclosed activity. As seen in the prior art cited in the International Search Report, the structural cores have different utility. See WO 01/ 14375, which teaches use of the pyrimidine compound of formula I for treating cancer. Thus more than one utility recited in the references cited in the Search Report of structurally related compounds negates the common distinct utility requirement.

Thus, both the above conditions for unity of invention are not met with.

In view of lack of unity of invention, the requirement for restriction for examination purpose is proper.

During a telephone conversion with Ms Lorie Ann Morgan on 10/24/2005, a provisional election was made with traverse to prosecute the invention of Group I, claims 1-7 and 9-22, compound of formula I where in Y is N. Affirmation of this election must be made by the applicant in replying to this office action. Claim 8 is withdrawn from further consideration by examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention. Claims 1-7 and 8-22 will be examined to the extent they embrace the elected subject matter.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one

or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Information Disclosure Statement

References cited in the Information Disclosure Statement, filed on, are made of record.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-7 and 9-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Following reasons apply. Any claim not specifically rejected is rejected as being dependent on a rejected claim and share the same limitation

1. Recitation of "physiologically functional derivative thereof" in claims 1, 13, 21 and 22 renders these claims and their dependent claims indefinite as it is vague and unclear as to what is embraced by the phrase. Reading specification page 20, last paragraph, the phrase appears to include esters and amides which would undergo transformation to active compound. But the phrase as interpreted appears to imply prodrug and would create ambiguity. Prodrugs in general and as noted in specification, are compounds, which undergo in vivo hydrolysis to parent active drugs. In that sense recitation of prodrug is acceptable. However, the definition of various variable groups include such

groups, namely esters, amides, alkoxycarbonyl etc. and therefore it is not clear what is the difference between these variable groups and the prodrug groups. There is clear-cut ambiguity as to what is to be considered as prodrug and what is not. Applicants should note that if the variable groups are prodrug, which are in general inactive but becomes active upon in vivo transformation, then the compound bearing the variable group would be deemed as inactive which is not what the claim recites.

Furthermore, the issue on second paragraph is whether the structures of the claimed compounds are clearly defined. Applicants' "physiologically functional derivative" are molecules whose structure lie outside the subject matter of formula (I), but upon metabolism in the body are converted to active compounds falling within the structural scope of formula (I). The claim describes the function intended but provides no specific structural guidance to what constitutes a "physiologically functional derivative". Structural formulas, names, or both can accurately describe organic compounds, which are the subject matter of claim 1. Attempting to define means by function is not proper when the means can be clearly expressed in terms that are more precise.

2. Claim 14 is indefinite as it appears to be a pharmaceutical composition but does not recite any other ingredient. A composition claim should have more than one ingredient.

3. Claim 22 is indefinite as it recites a process of converting compound of formula I or pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof to another compound of formula I or pharmaceutically acceptable salt, solvate

or physiologically functional derivative thereof. It is not clear what is being converted to what and what is the difference between claim 21 and claim 22. This is process claim and hence all essential steps should be clearly stated in the claim. As recited the claim is vague and unclear as to the process embraced.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7 and 9-22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making pharmaceutically acceptable salts does not reasonably provide enablement for making solvate. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The following apply.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1. **The nature of the invention and the state of the prior art:**

The invention is drawn to compound of formula I, or a pharmaceutically acceptable salt or solvate thereof. Specification is not adequately enabled as to how to make solvate of compounds of formula (I) Specification has no example of solvate of the instant compounds. Specification on page 20, lines 23-25, recites solvate thereof but there is no enabling of such compounds.

The compound of formula I embrace variously substituted pyrimidine bearing a pyrazolopyridine substituted with variable groups R^1, R^2, R^3, R^4 and R^5.

Even a cursory calculation of the number of compounds embraced in the instant formula (I) based on the generic definition of alkyl., aryl heteroaryl, heterocyclyl, substituted aryl, heteroaryl, arylalkyloxy, arylalkylthio etc would result in millions and millions of compounds. This is of course not the accurate number and the true number of compounds would far exceed this number of compounds. Thus the genus embraced in the claim 1 is too large and there is no teaching of any solvate of this large genus.

Search in the pertinent art, including water as solvent resulted in a pertinent reference, which is indicative of unpredictability of solvate formation in general. The state of the art is that is not predictable whether solvates or solvates will form or what their composition will be. In the language of the physical chemist, a solvate of organic molecule is an interstitial solid solution. This phrase is defined in the second paragraph on page 358 of West (Solid State Chemistry). The solvent molecule is a species introduced into the crystal and no part of the organic host molecule is left out or replaced. In the first paragraph on page 365, West (Solid State Chemistry) says, "it is not usually possible to predict whether solid solutions will form, or if they do form what is

the compositional extent". Thus, in the absence of experimentation one cannot predict if a particular solvent will solvate any particular crystal. One cannot predict the stoichiometery of the formed solvate, i.e. if one, two, or a half a molecule of solvent added per molecule of host. Compared with polymorphs, there is an additional degree of freedom to solvates, which means a different solvent or even the moisture of the air that might change the stabile region of the solvate. In the instant case of solvate a similar reasoning therefore apply. Water is a solvent and hence it is held that a pertinent detail of West, which relates to solvates, is also applicable to solvate

In addition, an additional search resulted in Vippagunta et al., Advanced Drug Delivery Reviews 48: 3-26, 2001, which clearly states that formation of solvates in unpredictable. See entire document especially page 18, right column section 3.4. Note Vippagunta et al., states "Each solid compound responds uniquely to the possible formation of solvates or hydrates and hence generalizations cannot be made for series of related compounds".

2. **The predictability or lack thereof in the art:**

Hence, the solvate and solvate as applied to the above-mentioned compounds claimed by the applicant are not art-recognized compounds and hence there should be adequate enabling disclosure in the specification with working example(s).

3. **The amount of direction or guidance present:**

Examples illustrated in the experimental section are limited to making the compounds not related to solvates and hydrates. There is no example of a solvate or hydrate of instant compound. Thirty-six compounds were shown in the examples of the

specification each of which has come in contact with water and other solvent but there is no showing that instant compounds formed solvates or hydrates. Hence it is clear that merely bring the compound with solvent or water does not result in solvate or solvate and additional direction or guidance is needed to make them Specication has no such direction or guidance.

4. **The presence or absence of working examples:**

There is no working example of any solvate or solvate formed. The claims are drawn to solvate, yet the numerous examples presented all failed to produce a solvate or hydrate. These cannot be simply willed into existence. As was stated in Morton International Inc. v. Cardinal Chemical Co., 28 USPQ2d 1190 "The specification purports to teach, with over fifty examples, the preparation of the claimed compounds with the required connectivity. However ... there, is no evidence that such compounds exist... the examples of the '881 patent do not produce the postulated compounds... there is ...' no evidence that such compounds even exist." The same circumstance appears to be true here. There is no evidence that solvates of these compounds actually exists; if they did, they would have formed. Hence, there should be showing supporting that solvates and solvates of these compounds exist and therefore can be made.

5. **The breadth of the claims & the quantity of experimentation needed:**

Specication has no support, as noted above, for compounds generically embraced in the claim 1 would lead to desired solvate and solvate of the compound of formula I. As noted above, the genus embraces over million of compounds and hence

the breadth of the claim is broad. The quantity of experimentation needed would be an undue burden on skilled art in the chemical art since there is inadequate guidance given to the skilled artisan for the many reasons stated above. Even with the undue burden of experimentation, there is no guarantee that one would get the product of desired solvate of compound of formula I embraced in the instant claims in view of the pertinent reference teachings.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here. Thus, undue experimentation will be required to make Applicants' invention..

Claims 1-7 and 9-22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making salts of the claimed compounds, does not reasonably provide enablement for making physiologically functional derivative of the claimed compounds. The claim(s) contains subject matter that was not described in the specification in such a way as to enable one skilled in the art of medicinal chemistry - to use the invention. "The factors to be considered in making an enablement rejection have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the

predictability or unpredictability of the art and the breadth of the claims", In re Rainer, 146 USPQ 218 (1965); In re Colianni, 195 USPQ 150, Ex parte Formal, 230 USPQ 546. a) Finding a prodrug is an empirical exercise. Predicting if a certain ester of a claimed alcohol, for example, is in fact a prodrug, and produces the active compound metabolically, in man, at a therapeutic concentration and at a useful rate is filled with experimental uncertainty. Although attempts have been made to predict drug metabolism 'de novo, this is still an experimental science. For a compound to be a prodrug or physiologically functional derivative, it must meet three tests. It must itself be biologically inactive. It must be metabolized to a second substance in a human at a rate and to an extent to produce that second substance at a physiologically meaningful concentration. Thirdly, that second substance must be biologically active. Thus, determining whether a particular compound meets these three criteria in a clinical trial setting requires a large quantity of experimentation.

The direction concerning the physiologically functional derivative is found in page 20, last paragraph. There is no working example of a physiologically functional derivative or prodrug of a compound the formula (I). The nature of the invention is clinical use of compounds and the pharmacokinetic behavior of substances in the human body. e) The state of the prodrug art is summarized by Wolff (Medicinal Chemistry). The table on the left side of page 976 outlines the research program to be undertaken to. find a prodrug. The second paragraph in section 10 and the paragraph spanning pages 976-977 indicate the low expectation of success. In that paragraph the difficulties of extrapolating between species are further developed. Since, the prodrug concept is a

pharmacokinetic issue, the lack of any standard pharmacokinetic protocol discussed in the last sentence of this paragraph is particularly relevant. Banker (Modem Pharmaceutics) in the first sentence, third paragraph on page 596 states that "extensive development must be undertaken" to find a prodrug. I) Wolff (Medicinal Chemistry) in the last paragraph on page 975 describes the artisans making Applicants' physiologically functional derivatives as a collaborative team of synthetic pharmaceutical chemists and metabolism experts. All would have a Ph. D. degree and several years of industrial experience. g) It is well established that "the scope of enablement varies inversely degree of unpredictability of the factors involved", 'and physiological activity is generally considered to be an unpredictable factor. See In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). h) The breadth of the claims includes all of the hundreds of thousands of compounds of formula of claim I as well as the presently unknown list potential prodrug derivatives embraced by the word "prodrug or physiologically functional derivative".

Thus, undue experimentation will be required to determine if any particular derivative is, in fact, a prodrug or physiologically functional derivative.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is

clearly justified here. Thus, undue experimentation will be required to make Applicants' invention.

Claims 20-22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compound of formula I wherein the X variable is chloro, bromo, iodo or triflate and groups R^2, R^3 and R^4 are not halogen or alkynyl group, does not reasonably provide enablement for compound of formula I wherein X variable is chloro, bromo, iodo or triflate and groups R^2, R^3 and R^4 are halogen. or alkynyl group. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The following apply:

In evaluating the enablement question, following factors are considered. Note In re Wands, 8 USPQ2d 1400 and Ex parte Forman, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1. The nature of the invention and the state of the prior art:

The invention of claim 20 and its dependent claims 21-22 are drawn to a process of making compound of formula I which involves coupling of compound of formula II wherein X is chloro, bromo, iodo or triflate with a terminal alkyne of formula III and then condensation of the resultant compound IV with N-aminopyridinum salt of formula V. Thus the first step which involves replacement of X with a alkyne can also occur if the

other substituents R^2, R^3 and R^4 are halogen . In addition, if these groups R^2, R^3 and R^4 are alkynes, they can then also participate in the subsequent condensation with N-aminopyridinium salts sated above.

Specification is not adequately enabled as to how to make compounds of formula I with above said choice of R^2, R^3 and R^4 groups which are either susceptible to coupling reaction when halogen or condensing reaction if they were alkynes. Specification offers no teachings or suggestion as to how to perform the said process of claims 20-22 with above said limitations and in presence of the reactive halogens or alkyne groups. Thus, presence of such reactive groups are chemically incompatible the process of coupling and condensation embraced in the instant claims.

2. The predictability or lack thereof in the art:

Hence the process as applied to the above-mentioned compounds claimed by the applicant is not an art-recognized process and hence there should be adequate enabling disclosure in the specification with working example(s).

4. The amount of direction or guidance present:

Examples illustrated in the experimental section or written description offer no guidance or teachings as to how perform the process of making compound of formula Ia when reactive substituents or chemically incompatible substituents are present in the starting material or how transform compound with said R^2, R^3 and R^4 are not halogen or alkynes.

5. The presence or absence of working examples:

Although examples in specification are limited to groups with no reactive functionality. There are no representative examples showing the viability of the process for plurality of reactive substituents embraced for R^2, R^3 and R^4.

6. The breadth of the claims:

Specification has no support, as noted above, for all compounds generically embraced in the claim language would lead to desired compound of formula Ia with said reactive groups and there is also no valid chemical reasoning for one trained in the art to expect that all the reactive functional groups would be inert toward the coupling and condensation reaction embraced in the process claim 20.

7. The quantity of experimentation needed:

The quantity of experimentation needed would be an undue burden on skilled art in the chemical art since there is inadequate guidance given to the skilled artisan for the many reasons stated above. Even with the undue burden of experimentation, there is no guarantee that one would get the product of desired structure, namely compound of formula Ia embraced in the instant claims in view of the prior art teachings of reactivity of these functional groups,.

Thus, factors such as "sufficient working examples", the "level of skill in the art and predictability, etc. have been demonstrated to be sufficiently lacking in the case for the instant claims.

MPEP §2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was 'filed, would not have taught one skilled in the art how to make

and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir.1993)." That conclusion is clearly justified here and undue experimentation will be required to practice Applicants' invention.

Claims 17-19 are rejected under U.S.C. 112, first paragraph, because the specification while being enabling for treating herpes viral infection due to HSV-1, does not reasonably provide enablement for treatment or prophylaxis of any herpes viral infections The specification does not enable any physician skilled in the art of medicine, to use the invention commensurate in scope with these claims..

The instant method of use claims 17-19 are drawn to "treatment or prophylaxis of herpes viral infection or treatment of a condition or disease associated with herpes viral infection in an animal in general. The scope of the claims includes any or all herpes viral infection or conditions and diseases due to inhibition HSV-1 including those yet to be discovered as due said mode of action for which there is no enabling disclosure. In addition, the scope of these claims includes treatment of various diseases, which is not adequately enabled solely based on the activity of the compounds provided in the specification at pages 64-67, example 37.. The instant compounds are disclosed to have HSV-1 inhibiting activity and it is recited that the instant compounds are therefore useful in treating any or all diseases stated above for which applicants provide no competent evidence. It appears that the applicants are asserting that the embraced compounds because of their mode action as inhibitor that would be useful for all sorts of herpes viral infection. However, the applicants have not provided any competent

evidence that the instantly disclosed tests are highly predictive for all the uses disclosed and embraced by the claim language for the intended host. The test provided in example 37 appears to be limited to HSV-1. There are no test procedures/assays provided to test the claimed compounds as antiviral agents for entire class herpes virus family.

The scope of the claims involves all of the thousands of compounds of claim 1 as well as the thousand of diseases embraced by the terms "a condition or a disease", as well as herpes viral infections in general.

In addition, instant claims also recite "prophylaxis and therefore , the instant claim language embraces not only treatment of the diseases and conditions and viral infections but also for prevention.

"To prevent" actually means *to anticipate* or *counter in advance, to keep from happening etc.* (as per Webster's II Dictionary) and there is no disclosure as to how one skilled in the art can reasonably establish the basis and the type of subject to which the instant compounds can be administered in order to have the "prevention" effect. There is no evidence of record which would enable the skilled artisan in the identification of the people who have the potential of becoming afflicted with the herpes viral infection in general or those specifically claimed herein Moreover many if not most of diseases herpes viral infections are very difficult to treat and despite the fact that there are many drugs, which can be used for viral inhibition and at present there is no known drug, which can successfully reverse the course of these infectious diseases, despite the fact that there are many antibacterial drugs, which can be used for "treating bacterial

infections". Note substantiation of utility and its scope is required when utility is "speculative", "sufficiently unusual" or not provided. See Ex parte Jovanovics, 211 USPQ 907, 909; In re Langer 183 USPQ 288. Also note Hoffman v. Klaus 9 USPQ 2d 1657 and Ex parte Powers 220 USPQ 925 regarding type of testing needed to support in vivo uses.

No compound has ever been found to treat herpes virus of all types generally. Since this assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits. The existence of such a "compound" is contrary to our present understanding of virology. There are more than 400 distinct viruses that infect humans producing a variety of diseases. Cecil Textbook of Medicine states, "for many viral infections, no specific therapy exists. Proper use of antiviral agents requires specific viral diagnosis and each specific type has unique biologic and clinical features that must be appreciated for proper diagnosis, treatment and study" (see the enclosed article, page 1742). The CDC website provides that " there is no treatment that can cure herpes" (http://www.cdc.gov/std/Herpes/STDFact-Herpes.htm). Thus, it is beyond the skill of oncologists today to get an agent to be effective against all herpes infections generally. Note substantiation of utility and its scope is required when utility is "speculative", "sufficiently unusual" or not provided. See Ex parte Jovanovics, 211 USPQ 907, 909; In re Langer 183 USPQ 288. Also note Hoffman v. Klaus 9 USPQ 2d 1657 and Ex parte Powers 220 USPQ 925 regarding type of testing needed to support in vivo uses.

Next, applicant's attention is drawn to the Revised Interim Utility and Written Description Guidelines, at 64 FR 71427 and 71440 (December 21, 1999) wherein it is emphasized that 'a claimed invention must have a specific and substantial utility'. The disclosure in the instant case is not sufficient to enable the instantly claimed method treating solely based on the inhibitory activity disclosed for the compounds. The state of the art is indicative of the requirement for undue experimentation. Note Bosseray et al. (PubMed Abstract enclosed) state that " Despite effective antiviral therapy HSV infections remain a public health problem". Razonable et al. (PubMed Abstract enclosed) indicate that "herpes virus infections continue to impact significantly on the outcome of transplantation" and "optimal preventive and treatment strategies for Epstein-Barr virus-related post-transplant lymphoproliferative disorders (PTLD) remain elusive". Only few of the references pertinent to the claims are discussed here to make the point of an insufficient disclosure, it does not definitely mean that the claims meet the enablement . requirements with respect to other members of herpes viruses.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1) The nature of the invention: A method for prophylaxis or treatment of herpes viral infections with instant compounds as well as in treating diseases/conditions that require viral inhibitory activity related HSV-1.

2) The state of the prior art: Recent publications expressed that the herpes viral inhibition effects are unpredictable and are still exploratory. See references cited above.

3) The predictability or lack thereof in the art: Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instant compounds for treating or preventing any or all conditions, diseases or any or all herpes viral infection. Note In re Surrey, 151 USPQ 724 regarding sufficiency of disclosure for a Markush group. Also see MPEP j 2164.03 for enablement requirements in cases directed to structure-specific Arts such as the pharmaceutical art. Receptor or enzyme activity is generally unpredictable and highly structure specific. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

4) The amount of direction or guidance present and 5) the presence or absence of working examples: Specification has no working examples to show treating any or all condition and the state of the art is that the effects of viral inhibitors are unpredictable.

6) The breadth of the claims: The instant claims embrace any or all herpes infection, conditions and disease mediated by herpes.

7) The quantity of experimentation needed would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan, regarding the pharmaceutical use, for the reasons stated above.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims. In view of the breadth of the claims, the chemical nature of the invention, the unpredictability of enzyme-inhibitor interactions in general, and the lack of working examples regarding the activity of the claimed compounds towards treating the variety of herpes viral infections and diseases of the instant claims, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims.

MPEP §2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was 'filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here and undue experimentation will be required to practice Applicants' invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-7, 9-12 and 14-16 are rejected under 35 U.S.C. 102(b) as being anticipated by Thomas et al., WO 01/14375

Thomas et al. teaches several substituted pyrimidine compounds which include instant compound of formula I and the composition. See entire document, especially see page 2, formula I. Note when A is second choice, namely pyrazolo[2,3a]pyri-3-yl, with the given definition of all other variable groups, the compounds taught by Thomas et al. include instant compounds. See page 24 for two schemes for making the compounds. See pages 36-57 for examples 1-98. Particularly see examples 14, 38, 96 and method 17 for various compounds made.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-7, 9-12 and 14-16 are rejected under 35 U.S.C. 103(a) as being unpatentable Thomas et al., WO 01/14375

Teachings of Thomas et al. as discussed in the above 102 rejection is incorporated herein. As noted above, Thomas et al. teaches several substituted pyrimidine compounds which include instant compound of formula I and the composition.

Thomas et al. differs in exemplifying large number of compounds wherein A is imidazo[1,2a]pyrid-3-yl ring and only few compounds with A as pyrazolo[2,3a]pyri-3-yl ring in the examples 1-98.

However, Thomas et al. teaches the equivalency of the two choices of A ring. compounds exemplified in the definition of A ring as noted in page 2.

Thus, it would have been obvious to one having ordinary skill in the art at the time of the invention was made to make pyrimidine compounds bearing imidazo[1,2a]pyrid-3-yl ring as well as pyrazolo[2,3a]pyri-3-yl ring as permitted by the

reference and expect resulting compounds (instant compounds) to possess the uses taught by the art in view of the equivalency teaching outline above.

Conclusion

Any inquiry concerning this communication from the examiner should be addressed to Venkataraman Balasubramanian (Bala) whose telephone number is (571) 272-0662. The examiner can normally be reached on Monday through Thursday from 8.00 AM to 6.00 PM. The Acting Supervisory Patent Examiner (SPE) of the art unit 1624 is James O. Wilson whose telephone number is (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAG. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-2 17-9197 (toll-free).

Venkataraman Balasubramanian

10/29/2005